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Essays in Biochemistry

Chronobiology

Edited by H. D. Piggins and C. Guilding

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Contents

Preface

Organisms from bacteria to humans use internal circadian [from the Latin '*circa*' ('around') and '*dian*' ('a day')] clocks to control daily biochemical, physiological and behavioural rhythms. The basis of this daily timing consists of: (i) input pathways that transduce external signals, such as changes in day length, to the clock; (ii) the pacemaker or clock itself, which is made up of molecular and biochemical feedback loops; and (iii) output pathways that allow the organism to co-ordinate the timing of cellular and behavioural process to specific times of day.

These systems synchronize the organism with both its internal and external environment, ensuring that the organism anticipates daily changes in environmental conditions and consequently displays the appropriate biochemistry, physiology and behaviour at the optimal time of day. Experimental evidence indicates considerable adaptive advantages in synchronization and alignment of circadian rhythms with the environment.

The study of biological timekeeping has exploded over the last 50 years, with many major research groups and scientific societies around the world (see Tables 1 and 2 for examples). As shown in Figure 1, 'circadian' as a key word is now associated with ~2500 publications a year.

This present *Essays in Biochemistry* volume ('Chronobiology') provides a broad perspective of key properties and characteristics of circadian biology across a range of species and demonstrates the ubiquitous and integral nature of chronobiology. Indeed, since this volume went to press, recent findings have highlighted unconventional 'non-clock gene' timekeeping biochemical mechanisms in both algae and human red blood cells [19,20].

Table 1. Circadian websites and societies

Name	Website URL
The Society for Research on Biological Rhythms	http://www.srbr.org/
European Biological Rhythms Society	http://www.ebrs-online.org/
Japanese Society for Chronobiology	http://wwwsoc.nii.ac.jp/jsc/index.html
European Sleep Research Society	http://www.esrs.eu/
EUCLOCK	http://www.euclock.org/
South African Society of Sleep Medicine	www.sassm.org
The Australasian Chronobiology Society	www.australasianchronobiology.org
Chinese Sleep Research Society	www.csrs.bj.cn
Indian Society for Sleep Research	http://www.issr.in

Table 2. Specialized journals

Name	Website URL
Journal of Biological Rhythms	http://jbr.sagepub.com/
Chronobiology International	http://informahealthcare.com/loi/cbi/
Biological Rhythm Research	http://www.tandf.co.uk/journals/titles/09291016.asp
Sleep and Biological Rhythms	http://www.wiley.com/bw/journal.asp?ref=1446-9235
Journal of Circadian Rhythms	http://www.jcircadianrhythms.com/

In Chapter 1, Hugh Piggins and Clare Guilding provide an overview of the circadian timing system in mammals. In Chapter 2, Nicholas Glossop outlines the genetic basis of the circadian clock in flies and mice, and in Chapter 3 Susan Crosthwaite describes the genetic basis of the circadian clock in model eukaryotic and prokaryotic organisms. In Chapter 4, Sally Adams and Isabelle Carré describe the circadian clockwork in plants and outline the output pathways used to rhythmically regulate functions, such as those of phytohormone synthesis and signalling. In Chapter 5, Ezio Rosato and Charalambos Kyriacou illuminate the adaptive value of circadian clocks, described by the reviewers

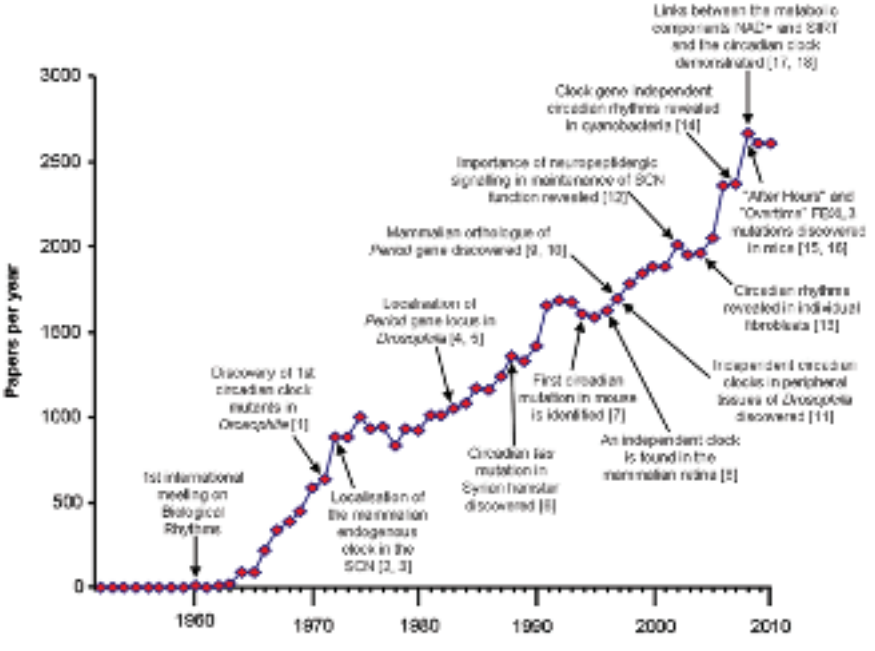

Figure 1. Number of papers published on circadian rhythms per year, with a range of significant events indicated.
Numbers were obtained by searching PubMed with the search term 'circadian' for each year.

as 'a very exciting, and underappreciated, aspect of circadian biology'. In Chapter 6, Charlotte Helfrich-Förster, Michael Nitabach and Todd Holmes examine how clock information is communicated throughout the insect brain and body. In Chapter 7, Christian Beaulé et al. provide an important assessment of the state-of-the-art in current models of circadian timekeeping in mammalian brain tissues. In Chapter 8, Ralph Mistlberger and Michael Antle examine how circadian rhythms in behaviour and physiology are regulated by environmental cues associated with arousal and appetite. This area has received considerable interest, as evidence for the neural substrates of food entrainment is contentious and hotly debated. In Chapter 9, Kalsbeek et al. focus on clock output in mammals and the importance of circadian timing in health and disease.

The editors would like to thank all the staff at Portland Press, in particular Clare Curtis for her dedication and hard work in producing this volume.

Hugh Piggins and Clare Guilding
Manchester, April 2011

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Authors

Hugh Piggins obtained a B.Sc. in Psychology at the University of Edinburgh and a Ph.D. in the neuropharmacology of neuropeptides at the University of Ottawa. Subsequently, he did postdoctoral training in circadian neurobiology with Benjamin Rusak and Kazue Semba at Dalhousie University. His laboratory in the University of Manchester focuses on *in vitro* studies of brain clocks, using electrophysiological, fluorescent and bioluminescent approaches. **Clare Guilding** obtained a B.Sc. in Neuroscience at the University of Edinburgh. She did her Ph.D. at the University of Edinburgh, investigating the effects of stress steroids on brain function and vestibular plasticity. Following two years of postdoctoral training at the University of Glasgow, she joined the laboratory of Hugh Piggins in 2005 where her work now focuses on circadian rhythmicity in stress and neuroendocrine-related areas of the brain.

Nicholas Glossop did his undergraduate degree in cell and molecular biology at the University of St. Andrews where he graduated in 1993 with first class honours. He then moved to Southampton and in 1997 received a postdoctoral degree from the University of Southampton for his thesis on the molecular basis of sensory axon guidance in *Drosophila*. He then spent the next six years in Houston, Texas, working on the *Drosophila* molecular clock. It was during this time that he discovered the interlocked-feedback-loop mechanism that, to this day, remains the standard model on which molecular clock research is based. In 2004, he moved back to England and is currently based at the University of Manchester, where he is a lecturer in developmental neurobiology.

Susan Crosthwaite initially became interested in circadian clocks during her Ph.D. studies on vernalization at the University of Glasgow. Intrigued by the cloning of the first *Neurospora* circadian clock gene in Jay Dunlap's laboratory, Dartmouth College, U.S.A., she joined Dunlap's group to embark on postdoctoral research into the molecular basis of the *Neurospora* clock and its resetting by light. The author currently has her own laboratory at the University of Manchester where she continues to study the *Neurospora* circadian clockwork, with a focus on non-coding RNAs.

Sally Adams carried out her Ph.D. studies at the University of Bath, where she investigated the role of DNA methylation in genomic imprinting in *Arabidopsis*. As part of her first postdoctoral position at the Friedrich Miescher Institute in Basel and the University of Geneva, she investigated the epigenetic basis of hybrid vigour. She then moved to the University of Leicester to examine chloroplast division in the unicellular green alga *Chlamydomonas*. This was followed by further projects looking at the modulation of flowering time

by light quality in *Arabidopsis*, and the integration of cold and light responses. She now works at the University of Warwick, where she uses a systems biology approach to investigate the global regulation of rhythmic transcription by the circadian clock. **Isabelle Carré** carried out her Ph.D. studies at the University of Stony Brook, where she studied the mechanism by which the circadian clock controls the timing of cell division in *Euglena*. She then moved on to the University of Virginia to investigate the regulation of circadian gene expression in *Arabidopsis*. She is now an Associate Professor at the University of Warwick, where she uses a combination of molecular, genetic and biochemical approaches to study the mechanisms underlying circadian rhythms and photoperiodic responses in plants. She collaborates with mathematicians, statisticians and bioinformaticians to: (i) investigate and model the function of gene networks underlying circadian oscillators and photoperiodic flowering, and (ii) decipher the regulatory logic within gene promoters that underlies specific temporal patterns of transcription.

Charalambos Kyriacou has been working in behavioural genetics since 1973, and on circadian rhythms since 1978 when he joined Jeff Hall's laboratory at Brandeis University and was involved in the early molecular work on the *period* gene with collaborators Hall and Michael Rosbash. He has largely focused on the more evolutionary and ecological aspects of circadian genetics with Rudi Costa at the University of Padova and, more recently, with Eran Tauber, another former postdoctoral associate, at the University of Leicester. He also works on circadian 'omics' with his collaborators Michael Hastings and Kathryn Lilley at the University of Cambridge and on crustacean rhythms with Hastings and Simon Webster (University of Bangor). **Ezio Rosato** is a former postdoctoral associate of Charalambos Kyriacou, and they share facilities and laboratory space. His main interests focus on the biology of the cryptochrome circadian photoreceptor in *Drosophila*, and his approach involves molecular and neurobiological approaches. He also is interested in rhythms in krill.

Todd Holmes is Professor of Physiology and Biophysics at the University of California at Irvine School of Medicine. His research group works on the light-activation of neurons and the physiology of circadian and arousal neural circuits and how these circuits dictate behaviour in *Drosophila melanogaster*. **Michael Nitabach** is Associate Professor of Cellular and Molecular Physiology and Associate Professor of Genetics at the Yale School of Medicine, Yale University. His laboratory applies genetic, molecular, cellular, systems biology and physiological approaches to understanding the neural control of behaviour. **Charlotte Helfrich-Förster** is Professor of Neurobiology and Genetics at the University of Würzburg. Her research focuses on the circadian clock of *Drosophila melanogaster* and the synchronization to external *Zeitgebers*.

Erik Herzog grew up in Madison, Wisconsin, U.S.A. After studying Biology and Spanish at Duke University, he worked as a SCUBA diver for 2 years and then went to Syracuse University to study under Robert Barlow. During his Ph.D. research, he became fascinated by the circadian oscillators that help horseshoe crabs see equally well during the day and at night. This led him to undertake postdoctoral research at the University of Virginia with Gene Block. Since 2000, Erik Herzog and his collaborators at Washington University in St. Louis have been studying the cellular basis for circadian rhythms in mammals. **Christian Beaulé** grew up in the province of Québec, Canada. He obtained a B.Sc. in Psychology with a specialization in Psychobiology from Concordia University. He then stayed at Concordia University and obtained a Ph.D. in Psychology working with Shimon Amir on the mechanism responsible for entrainment of circadian rhythms by light. This led him to the University of Illinois at Urbana-Champaign where he undertook postdoctoral work for 3 years with Martha U. Gillette, studying circadian rhythms *in vitro*. Christian Beaulé then moved to Washington University in Saint Louis to do postdoctoral work with Erik Herzog, studying circadian rhythms in astrocytes. **Daniel Granados-Fuentes** grew up in Mexico City. After studying Biology, he obtained an M.Sc. and a Ph.D. in Physiology from the Universidad Nacional Autonóma de México, working with Raul Aguilar-Roblero. His first experiences with circadian biology were during college, where he was studying the physiological regulation of sleep in humans; this made him switch areas to start studying the interaction of different afferents with the circadian clock in mammals. Daniel moved to Washington University in St. Louis to continue studying with Erik Herzog the cellular basis for circadian rhythms in the suprachiasmatic nucleus and the olfactory bulb. **Luciano Marpegan** grew up in Bariloche, Argentina. He studied Biology at Buenos Aires University, where he obtained his Ph.D. directed by Diego Golombek. As an undergraduate, he worked in Patagonia studying the relationship between the parasitic fungus *Cyttaria sp*. and its host tree *Nothofagus sp.*, becoming interested in microscopy and cell-culture techniques. In 1995, he became interested in chronobiology, working first on the relationship between the immune and circadian systems, then on the role of astrocytes in such interactions. Luciano Marpegan joined Erik Herzog's team in 2005 to study the role of astrocytes in the circadian system.

Ralph Mistlberger holds degrees from McGill University (B.A., 1979) and the University of Chicago (Ph.D., 1984) and conducted postdoctoral research at Dalhousie University and Harvard Medical School before joining the Department of Psychology at Simon Fraser University in 1988, where he is now Professor. His work on circadian rhythms and sleep is supported by the Natural Sciences and Engineering Research Council of Canada and by the Canadian Institutes for Health Research. **Michael Antle** holds degrees from

Dalhousie University (B.Sc., 1995) and Simon Fraser University (Ph.D., 2001) and conducted postdoctoral research at Columbia University before joining the University of Calgary in 2004, where he is now Associate Professor with a joint appointment in the Departments of Psychology and Physiology and Pharmacology, and a member of the Hotchkiss Brain Institute. His work on circadian rhythms is supported by the Natural Sciences and Engineering Research Council of Canada.

Andries Kalsbeek is team leader of the Hypothalamic Integration Mechanisms group at the Netherlands Institute for Neuroscience (NIN) and Head of the Department of Experimental Endocrinology at the Academic Medical Center (AMC) in Amsterdam, The Netherlands. He obtained his M.Sc. (1984) at the University of Groningen. After his Ph.D. (1989), he started working on the output mechanisms of the biological clock and the hypothalamic control of energy metabolism, first as a postdoctoral fellow with Paul Pévet in Strasbourg, France, and subsequently as a senior researcher in the NIN group of Ruud Buijs. Since 2005, he has been heading his own group. **Chun-Xia Yi** is a postdoctoral fellow in the NeuroEndocrinology, Obesity & Nutrition (NEON) laboratory in Cincinnati headed by Matthias Tschöp. She obtained her Ph.D. in the Hypothalamic Integration Mechanisms group headed by Andries Kalsbeek at the NIN. During her Ph.D., she studied the metabolic-sensing mechanisms of the biological clock and the role of the hypothalamus in the control of hepatic glucose production. In her current research project in Cincinnati, she aims to combine targeted mouse mutagenesis and novel specific pharmacological tools to dissect the involvement of central glucagon-receptor signalling in peripheral metabolic homoeostasis. **Cathy Cailotto** is a postdoctoral fellow in the Tytgat Institute for Liver and Intestinal Research at the AMC, Amsterdam. She obtained her Ph.D. in the NIN at the University of Amsterdam. During her Ph.D., she studied the role of the biological clock and peripheral clock genes in the genesis of the daily glucose rhythm under the supervision of Andries Kalsbeek, Paul Pevet and Ruud Buijs. Currently, she is working on the gut–brain interactions during an immune challenge, with a particular interest for the cholinergic anti-inflammatory pathway. **Susanne la Fleur** is a Scientific Staff Member in the Department of Endocrinology and Metabolism, AMC, Amsterdam. She received a Ph.D. in Neuroscience in 2001 following a research period at the Netherlands Institute for Brain Research (Amsterdam) on the regulation of the daily rhythm in plasma glucose, and hypothalamus–liver interactions. She did her postdoctoral research with Mary Dallman at the University of California, San Francisco. In 2004, she started her own research line at the Rudolf Magnus Institute of Neuroscience, focusing on the central nervous system integration of (nutritional) information important for the development of obesity and associated disorders. In 2008, her research group relocated to

Amsterdam. **Eric Fliers** is Professor of Endocrinology at the University of Amsterdam, serving as chief of the Division of Endocrinology and Metabolism at the AMC, Amsterdam. He received his Ph.D. in 1985 after studying the functional neuroanatomy of neuroendocrine nuclei in the human hypothalamus, and his M.D. (with honours) in 1987, both from the University of Amsterdam. Fliers was subsequently trained as an internist-endocrinologist (board certification in 1992). His current research interests include the neuro-endocrine response to (psychiatric) illness, and novel neural pathways for metabolic effects of thyroid hormone. Eric Fliers is a Board member of the Dutch Endocrine Society. **Ruud Buijs** is Professor of Neurobiology and research leader at the Instituto de Investigaciones Biomedicas, UNAM Mexico. He obtained his Ph.D. at the University of Amsterdam in 1980 and was appointed at the Netherlands Institute for Brain Research in Amsterdam. In 1990, he accepted a position at the Loeb Research Institute in Ottawa and returned to the Netherlands Institute for Brain Research in 1993 to become Associate Director and leader of the group 'Hypothalamic Integration Mechanisms'. At the same time, he was appointed Professor of Neurobiology at the University of Amsterdam until he moved to Mexico in 2006.

Abbreviations

ABA	abscisic acid
ABAR	*ABA-related*
ABI3	ABA-INSENSITIVE 3
ABREL	ABA response element-like
AM	amplitude modulation
aMe	accessory medulla
AMPK	AMP-activated protein kinase
ANS	autonomic nervous system
AP	action potential
ARC	arcuate nucleus
AtGRP7	*Arabidopsis thaliana* GLYCINE-RICH PROTEIN 7 [also known as CCR2 (COLD, CIRCADIAN RHYTHM AND RNA-BINDING 2)]
AVP	arginine vasopressin
bHLH	basic helix–loop–helix
bHLH-PAS	basic HLH-Per-Arnt-Sim
Bmal1	*brain and muscle arnt-like 1*
bZIP	basic leucine zipper
CCA	*CIRCADIAN CLOCK-ASSOCIATED*
CBS	CCA1-binding site
CCG	clock-controlled (output) gene
CDF1	CYCLIC DOF FACTOR 1
CHE	CCA1 HIKING EXPEDITION
ChIP-Seq	chromatin immunoprecipitation-sequencing
cikA	*circadian input kinase* gene
CK	casein kinase
CLK	CLOCK (circadian locomotor output cycles kaput)
CNS	central nervous system
CO	CONSTANS
COP1	CONSTITUTIVE PHOTOMORPHOGENIC 1
CR	coevolving region
CRH	corticotrophin-releasing hormone
CRY	CRYPTOCHROME
cry1-2	cryptochrome gene
CT	circadian time
CWO	CLOCKWORK ORANGE
CYC	CYCLE
dbp	*albumin D-box binding protein*

DBT	Doubletime
DD	constant dark
Dec	*deleted in esophageal cancer*
Dexras1	dexamethasone-induced Ras-related protein 1
DMH	dorsomedial nuclei of the hypothalamus
DN	dorsal neuron
DN1p	posterior DN, group 1
e4bp4	*adenovirus E4 promoter ATF-site-binding*
EE	Evening Element
EEL	EE-like
EGFP	enhanced destabilized green fluorescent protein
ELF	EARLY FLOWERING
ERK1/2	extracellular-signal-regulated kinase 1/2
E-vector	electric vector
FEO	food-entrainable circadian oscillator
FFC	FRQ/FRH complex
FIO	FIONA
FKF1	FLAVIN-BINDING, KELCH REPEAT, F-BOX 1
FM	frequency modulation
frq	*frequency*
FRH	FRQ-interacting helicase
FT	*FLOWERING LOCUS T*
FWD-1	F-box/WD-40-repeat-containing protein
GABA	γ-aminobutyric acid
GFP	green fluorescent protein
GHT	geniculohypothalamic tract
GI	GIGANTEA
GnRH	gonadotropin-releasing hormone
GRP	gastrin-releasing peptide
GSK1	glycogen synthase kinase 1
hlf	*hepatic leukaemia factor*
HPA	hypothalamo–pituitary–adrenal
5-HT	5-hydroxytryptamine (serotonin)
HUD	Hormone Up at Dawn
IGL	intergeniculate leaflet
ipRGC	intrinsically photosensitive RGC
LD	light–dark
lFRQ	large FRQ
LH	luteinizing hormone
LHCB	*light-harvesting chlorophyll a/b binding*
LHY	*LATE ELONGATED HYPOCOTYL*
LIP	LIGHT-INSENSITIVE PERIOD
LL	constant light

LNd	dorsolateral neuron
LNv	ventrolateral neuron
l-LNv	large LNv
lpdA	*light-dependent period* gene
luc	luciferase
LUX	LUX ARRHYTHMO
LWD	LIGHT-REGULATED WD
M and E	'morning and evening'
MAPK	mitogen-activated protein kinase
MCH	melatonin-concentrating hormone
MEA	multi-electrode array
MP	membrane potential
MPOA	medial pre-optic area
MR	median raphe
Npas2	neuronal *pas-2*
NPY	neuropeptide Y
PACAP	pituitary adenylate cyclase-activating polypeptide
PBAN	pheromone biosynthesis-activating neuropeptide
PCL	PHYTOCLOCK
pCLK	phosphorylated CLK
PDF	PIGMENT-DISPERSING FACTOR
PDFR	PDF receptor
PDP1ε	PAR DOMAIN PROTEIN 1ε
PER	PERIOD
per	*period* gene
pex	*period extender* gene
PGC-1α	PPARγ co-activator 1α
PIF	phytochrome-interacting factor
PK2	prokineticin 2
PKA	protein kinase A
PP	protein phosphatase
PP2A	PROTEIN PHOSPHATASE 2A
PPAR	peroxisome proliferator-activated receptor
pPER	phosphorylated PER
PRC	phase–response curve
prd	*period 1-4*
PRR7	*PSEUDO-RESPONSE REGULATOR 7*
PVN	paraventricular nuclei
RGC	retinal ganglion cell
RHT	retinohypothalamic tract
RNAi	RNA interference
RpaA	phycobilisome-associated protein

RRE	Rev-erbα and retinoic-acid-related element
RVE1	REVEILLE 1
SasA	*Synechococcus* adaptive sensor protein
SCF	Skp1/cullin/F-box
SCN	suprachiasmatic nuclei
sFRQ	small FRQ
SGG	Shaggy
SIRT1	sirtuin 1
s-LNv	small LNv
SP	substance P
subPVN	subparaventricular zone
TCP	TEOSINTE BRANCHED1, CYCLOIDEA and PCF
tef	*thyrotroph embryonic factor*
TGF	transforming growth factor
TIC	TIME FOR COFFEE
TIM	TIMELESS
tim	*timeless* gene
TOC	*TIMING OF CAB*
TSF	*TWIN SISTER OF FT*
TTFL	transcriptional–translational feedback loop
TTX	tetrodotoxin
VIP	vasoactive intestinal polypeptide
VMH	ventromedial hypothalamus
VRI	VRILLE
wc	*white collar*
WCC	WHITE COLLAR complex
XCT	XAP5 CIRCADIAN TIME KEEPER
ZT	*Zeitgeber* time
ZTL	ZEITLUPE